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Risk Factors for Thrombosis in Nonembolic Cerebrovascular Disease

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Thirty-seven young patients (less than 42 years of age) presenting with sudden onset of idiopathic nonembolic cerebrovascular disease were evaluated for underlying prothrombotic factors. Activated protein C resistance (APC-R) was measured by Dahlback's method and the modified method using factor V-deficient plasma. Activities of antithrombin (AT) III, protein C and S were measured. Anticardiolipin antibody was estimated by ELISA and lupus anticoagulant by kaolin clotting tests.

APC-R was the most common defect (21.62%) followed by AT III deficiency and presence of anticardiolipin antibodies (5.6% each). The latter two were present together in one case. It is thus concluded that APC-R is the most common defect underlying idiopathic nonembolic cerebrovascular infarction in young individuals. Am. J. Hematol. 60:239–241, 1999. © 1999 Wiley-Liss, Inc.

Key words: risk factors; nonembolic cerebrovascular disease

INTRODUCTION

Nonembolic cerebral arterial (NECA) infarction is a challenging problem in young individuals because its etiology remains largely undetermined. Although antiphospholipid antibodies are found in these, hereditary defects of antithrombotic proteins are seldom seen [1]. Recently, activated protein C resistance (APC-R) has been implicated in venous thrombosis. Its role in the pathogenesis of NECA infarction is unclear. In the present study, we evaluated the prothrombotic parameters in young individuals with NECA infarction.

MATERIALS AND METHODS

Subjects

Young patients (less than 42 years of age) presenting with sudden onset of stroke to the Neurology Department at the All India Institute of Medical Sciences, New Delhi, India, were the subjects. A history of smoking, oral contraceptive use, recent pregnancy or prolonged bed rest and presence of diabetes mellitus and hypertension were prohibited factors in all patients. CT scan and MRI examination of the skull were done in all patients to identify the area of infarction.

Laboratory Evaluation

Citrated platelet poor plasma was tested for various prothrombotic parameters. APC-R was determined by performing the Dahlback's APC test using APC from Diagnostica Stago, France [2], and modified APC resistance test was performed using factor V (FV)-deficient plasma [3]. The result was expressed as normalized APC sensitivity ratio (nAPC-SR). Its normal range in our lab was 0.76 to 1.12 (mean = 0.94; SD = 0.089) by Dahlback's method and 0.79 to 1.02 (mean = 0.92; SD = 0.062) by the modified APC test. Activities of protein C and S were measured using kits from Diagnostica Stago, France. Thrombin-based coagulation assay was performed to measure the functional activity of antithrombin (AT) III [4]. Its normal range was 75–125 U/dl.

Quantification of immunoglobulin (Ig)G anticardiolipin antibodies (ACA) was done by commercial ELISA kit (ORGenTec, Diagnostika GmbH, Germany). A value greater than 7 GPL U/ml was considered abnormal. Lu-

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TABLE I. Relative Prevalence of Hemostatic Defects Underlying Young Nonembolic Cerebral Arterial Infarctions*

Patients with cerebrovascular disease	AT III activity U/dl	Protein C activity 70–130% NPP	Protein S activity 65–140% NPP	LAC	ACA <7 = N GPL U/ml	APC resistance by modified APC test nAPC-SR ⩽0.79
n = 37	2	Nil	Nil	Nil	2	8
	5.4%	Nil	Nil	Nil	5.4%	21.62%

*AT III, antithrombin III; NPP, normal pooled plasma; LAC, lupus anticoagulant; ACA, anticardiolipin antibodies; GPL, IgG phospholipid; APC, activated protein C; SR, sensitivity ratio.

pus anticoagulant (LA) was detected by presence of prolonged kaolin clotting time (KCT > 120 sec), which did not correct on addition of equal amounts of normal plasma to test plasma but corrected on inosithin addition [5].

RESULTS

Thirty-seven patients (3 months–42 years; m:f = 23:14) were diagnosed with NECA infarction. Thrombosis was confirmed in the middle cerebral artery in 21 (51.7%) patients and vertebral artery in three (8.1%) patients. Infarction was detected in the parietal lobe in five (13.5%) patients, frontal lobe in five (13.5%) patients, and occipital lobe in three (8.1%) patients. Because cardiac source of embolism was excluded by absence of valvular and cardiac disease on echocardiogram in all cases, these were considered due to thrombosis.

Of the 37 patients, APC-R was the most common defect seen in eight (21.6%) patients. Elevated ACA was seen in two (5.4%) patients (20 and 25 GPL μ/ml, IgG, respectively). AT III deficiency occurred in two (5.4%) patients (62 and 64 μ/dl, respectively); one of whom also had raised ACA levels (25 GPL μ/ml, IgG). None of the patients had protein C or protein S deficiency or presence of LA (Table I).

APC-R was detected in four (10.8%) patients by classical Dahlback's test and in eight (21.62%) patients by the modified APC test. The latter, being more sensitive and specific for FV Leiden defect than the classic APC test [6], was taken to be the indicator of true prevalence of APC-R. All the patients resistant to APC by classic test, were also found to have APC-R by the modified APC test. None of these patients had associated antiphospholipid antibodies or antithrombotic protein deficiency.

DISCUSSION

The role of coagulation factors in altering the coagulability of the blood in arterial thrombosis is not well documented. In the present study we observed the presence of APC-R to be the most common predisposing factor in young NECA infarction patients. The prevalence of APC-R in 21.6% of young patients with NECA infarction is higher than that found in the general Indian population (1.9%) [7] but lower than that in deep vein thrombosis (39.2%) [8].

This was, however, higher than the 4% prevalence of APC-R, reported in other studies on idiopathic arterial thrombosis [9]. This may be due to the inclusion of nonembolic cerebral arterial infarct cases instead of all the arterial diseases in our study, or because a more sensitive modified APC test was used to detect APC-R in the present study. Moreover, in our study, patients were less than 42 years of age, in contrast to the study of Cushmann et al. [9] on patients less than 55 years. Our results are comparable to those of Halbmayer et al. [10] who observed APC-R in 17.5% of patients with juvenile recurrent ischemic cerebral disease. Mild AT III deficiency was seen as an isolated prothrombotic defect in one case but associated with elevated ACA in our remaining cases. Primary AT III deficiency leading to cerebrovascular disease in this case appears unlikely since it is usually implicated in venous thrombosis. The presence of associated ACA may have contributed to arterial thrombosis in the second patient.

Brey et al. [1] reported the presence of APA in 46% patients (under 50 years) with a history of cerebral ischemia. Twenty percent of these patients had mitral valve anomalies. The lower prevalence of ACA (5.4%) observed in the present series may be because of the strict selection criteria used in our cases to exclude patients with underlying cardiac abnormalities and those older than 42 years. Absence of proteins C and S in these cases was not unusual because these defects usually underlie venous thrombosis.

It is thus concluded that APC-R is the most common cause of idiopathic nonembolic cerebrovascular infarction in young patients. Its detection along with presence of antiphospholipid antibodies is important in identification of cases who would benefit from adjuvant anticoagulant therapy.

REFERENCES

1. Brey RL, Hart RG, Sherman DG, Tegeler CH. Antiphospholipid antibodies and cerebral ischemia in young people. Neurology 1990;40: 1190.
2. Dhalback B, Carlsson M, Svensson PJ. Familial thrombophilia due to a previously unrecognised mechanism characterised by poor anticoagulant response to activated protein C—prediction of a cofactor to activated protein C. Proc Natl Acad Sci 1993;90:1004.
3. Trossaent M, Conarcl J, Horrelou MH, Samaina MM, Ireland H, Bayston TA, Lane DA. Modified APC resistance assay for patients on oral anticoagulants. Lancet 1994;344:1709.
4. Dacie JV, Lewis SM. Practical haematology. Edinburgh: Churchill Livingstone, 8th ed. 1994.
5. Saxena R, Saraya AK, Kotte VK, Singh YN, Prasad L, Malviya AN. Inosithin neutralisation test for quantitation of LA. Am J Clin Pathol 1993;99:61.
6. Jorquera JI, Montoro JM, Fernandez MA, Aznar JA, Aznar J. Modified test for activated protein C resistance. Lancet 1994;344:1163.
7. Garewal G, Das R, Trehan U. Factor V prevalence in the indigenous population and cases of thrombosis in North India. Br J Haematol 1997;97:940.
8. Saxena R, Mohanty S, Srivastava A, Choudhry VP, Kotwal J. Activated protein C (APC) resistance in Indian juvenile deep vein thrombosis. Thromb Res 1998 (in press).
9. Cushman M, Bhushan F, Bovil E, Tracy R. Plasma resistance to activated protein C in venous and arterial thrombosis. Thromb Haemost 1994;72:643.
10. Halbmayer WN, Haushofer A, Schon R, Fisher M. Prevalence of poor anticoagulant response to activated protein C (APC resistance) among patients suffering from non-embolic cerebral arterial infarction or venous thrombosis and among healthy subjects. Blood Coagul Fibrinolysis 5:51, 1994.